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RESEARCH ARTICLE

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Association of single nucleotide polymorphisms in *resistin* gene with rheumatoid arthritis in a Chinese population

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Background: Recent evidences have revealed that resistin is associated with the development of rheumatoid arthritis (RA). The aim of this study was to analyze the association of *resistin* gene single nucleotide polymorphisms (SNPs) with RA susceptibility.

Methods: In this study, we finally analyzed three *resistin* SNPs (rs1862513, rs3745368, and rs3745367) in 278 RA patients and 276 normal controls recruited from Chinese population using TaqMan SNP genotyping assays.

Results: There were no significant differences for the distribution of allele and genotype frequencies of these three SNPs between RA patients and normal controls (all $P > .05$). The genotype effects of dominant, recessive models were also analyzed, and no significant association was detected (all $P > .05$). Haplotype analysis suggested that the frequency of haplotype GAA was notably lower in RA patients in comparison with normal controls (OR = 0.317, 95% CI: 0.125-0.807, $P = .011$).

Conclusion: In a ward, our results indicated that *resistin* gene polymorphisms might affect the genetic predisposition of RA in Chinese population.

KEYWORDS
adipokine, resistin, rheumatoid arthritis, single nucleotide polymorphisms

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder, characterized by chronic inflammation of the joints which may arouse enormous inflammation in the synovium, and the permanent destruction to joint cartilage and bone.[1] Although, the incidence of RA is approximately 1% in the world, the precise mechanism of this disease is still unclear. As the exciting discovery of the precise properties of adipokines, the associations between adipokines and RA and the understanding of the potential mechanism have attracted attention. Adipokines are predominantly secreted by white adipose tissue, which is known as a primary endocrine organ in humans.[2] Moreover, stimulated articular adipose tissue would highly produce classical adipokines and a wide range of pro-inflammatory and anti-inflammatory cytokines.[3] Studies have demonstrated that adipokines, which have the function to modulate various processes including inflammatory and metabolism, might be involved in the pathophysiology of obesity-related diseases including RA.[4-6] Increased adipokine levels were also found in the plasma and synovial fluid from RA patients, and the results implied that adipokines were involved in the pathogenesis of RA by exerting effective modulatory effects on target tissues and cells including cartilage, synovium, bone, and various immune cells.[7,8]

Resistin (resistance to insulin) is initially found to be produced by murine adipocytes and could improve insulin resistance.[9] Moreover, inflammatory cytokines are shown to induce resistin synthesis in human monocytes.[10] Because of the ability of resistin to the activate NF-κB-dependent pathways to secrete tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and IL-1β in human peripheral blood mononuclear cells, and increase MAPK activation,[11,12] resistin is perceived as a pro-inflammatory cytokine and might instead be

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involved in inflammatory processes rather than in the modulation of glucose homeostasis in humans.[5] Previous evidences suggested that resistin level in plasma was correlated strongly with several inflammatory markers including C reactive protein (CRP), IL-6.[13] In RA patients, resistin was found increased in the synovium when compared to these with osteoarthritis, and significantly associated with several inflammatory markers including CRP and erythrocyte sedimentation rate (ESR).[14] Furthermore, healthy mouse when injected recombinant resistin into knee joints was also shown to induce leukocyte infiltration and hyperplasia of the synovial, which was similar to the pathology of RA.[11]

These findings had shown that resistin might have a potential role in RA pathogenesis, and aberrant serum levels of resistin were found in RA sufferers,[15,16] while few studies had discussed the relationship between *resistin* gene variation and RA risk. On this basis, we carried out this study to investigate whether *resistin* gene polymorphisms (rs1862513, rs3745368, and rs3745367) are connected with RA susceptibility in a Chinese population.

2 | STUDY SUBJECTS AND METHODS

2.1 | RA patients and normal controls

In this study, we initially recruited 288 RA patients and 288 normal controls. All the patients, who recruited from the Department of Rheumatology at the First Affiliated Hospital of University of Science and Technology of China and the First Affiliated Hospital of Anhui Medical University, met the American College of Rheumatology (ACR) criteria.[17] The normal controls with no history of chronic inflammatory or autoimmune diseases were recruited from the general population and healthy blood donors. The patients' clinical features, comprised anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF), were obtained through reviewing medical records. RF was detected by a turbidimetric assay according to the manufacturer's instructions; individual with serum values ≥20 U/mL was regarded as RF positive, and <20 U/mL was regarded as RF negative. Anti-CCP was measured with enzyme-linked immunosorbent assay; individual with serum values ≥25 U/mL was considered as anti-CCP positive, while those <25 U/mL was considered as anti-CCP negative. All the subjects were enrolled after informed consent had been obtained, and this study protocol was approved by the Medical Ethics Committee of Anhui Medical University.

2.2 | DNA extraction and SNP genotyping

Blood samples (5 mL) were collected from each subject, and genomic DNA was isolated from the peripheral blood leukocytes by the standard procedures with the Flexi Gene-DNA Kit (Qiagen, Valencia, CA).

The SNPs were genotyped by Fluidigm® 192.24 Dynamic Array IFC (Integrated Fluidic Circuit) (Fluidigm Corp, South San Francisco, CA, USA) using TaqMan SNP Genotyping Assay Kit. Only those with 100% genotype success rate for all SNPs were included for analysis; thus, we finally analyzed the three resistin SNPs (rs1862513, rs3745368, and rs3745367) in 278 RA patients and 276 normal controls.

2.3 | Statistical analysis

The Hardy-Weinberg equilibrium for normal controls was assessed using chi-square (χ^2) test. The statistical power was determined using the Power and Sample Size Calculation Software (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize). The differences in genotype and allele frequencies of all SNPs in RA patients and normal controls were analyzed by chi-square (χ^2) or Fisher exact. Odds ratios (OR) and 95% confidence interval (CI) were evaluated by logistic regression analyses. Haplotype analysis was evaluated by the SHEsis software (http://analysis.bio-x.cn/myAnalysis.php).[18] Above statistical analyses were performed using the SPSS 10.01 (SPSS Inc., IL, USA), and *P* value (two-sided) <.05 was considered as statistically significant.

3 | RESULTS

There were 44 males and 234 females in RA sufferers with an average age of 53.85 ± 12.77 years and 130 males and 146 females in normal controls with an average of 55.18 ± 15.20 years. According to the status of anti-CCP and RF, the RA patients could be categorized as different serotypes. We found 234 (84.2%) patients were diagnosed with anti-CCP positive, and 229 (82.4%) patients were diagnosed with RF positive, respectively. The genotype distributions of rs1862513, rs3745368, and rs3745367 in normal controls were in accordance with Hardy-Weinberg equilibrium (all $P > .05$). The power was approximately 66.1% for rs1862513, 47.7% for rs3745368, and 64.5% for rs3745367 ($\alpha = .05$, OR = 1.5).

3.1 | The associations between *resistin* gene rs1862513, rs3745368, and rs3745367 polymorphisms and RA susceptibility

The genotype and allele frequencies of rs1862513, rs3745368, and rs3745367 in RA patients and normal controls were represented in Table 1. There were no significant differences in genotype distributions of all SNPs polymorphism between RA patients and normal controls (all $P > .05$). Similarly, no significant findings regarding the allele frequencies of all SNPs were observed (all $P > .05$). In addition, the association of *resistin* gene variation with RA under two main genetic models including dominant, recessive models was also analyzed, and the results were still not significant (all $P > .05$).

3.2 | The associations of *resistin* gene rs1862513, rs3745368, and rs3745367 polymorphisms with risk of different serotypes of RA

We carried out a case-only study to evaluate the associations of *resistin* gene rs1862513, rs3745368, and rs3745367 polymorphisms

TABLE 1 Genotype and allele frequencies of *resistin* gene in RA patients and controls

SNP	Analyze model	RA patients (N = 278) n (%)	Control (N = 276) n (%)	*P* value	*OR* (95% *CI*)
rs1862513	Genotype				
	CC	120 (43.2)	109 (39.5)	.145	0.656 (0.372-1.157)
	GC	132 (47.5)	131 (47.5)	.243	0.717 (0.410-1.254)
	GG	26 (9.3)	36 (13.0)	Reference	
	Allele				
	C	372 (66.9)	349 (63.2)	.199	1.176 (0.918-1.506)
	G	184 (33.1)	203 (36.8)	Reference	
	Dominant model				
	CC	120 (43.2)	109 (39.5)	.380	1.164 (0.829-1.632)
	GG+GC	158 (56.8)	167 (60.5)	Reference	
	Recessive model				
	GC+CC	252 (90.6)	240 (87.0)	.168	1.454 (0.852-2.481)
	GG	26 (9.4)	36 (13.0)	Reference	
rs3745368	Genotype				
	GG	204 (73.4)	193 (69.9)	.390	0.631 (0.220-1.805)
	GA	68 (24.5)	74 (26.8)	.562	0.725 (0.245-2.145)
	AA	6 (2.1)	9 (3.3)	Reference	
	Allele				
	G	476 (85.6)	460 (83.3)	.295	0.840 (0.607-1.164)
	A	80 (14.4)	92 (16.7)	Reference	
	Dominant model				
	GG	204 (73.4)	193 (69.9)	.367	0.843 (0.583-1.221)
	AA+GA	74 (26.6)	83 (30.1)	Reference	
	Recessive model				
	GA+GG	272 (97.8)	267 (96.7)	.424	0.654 (0.230-1.864)
	AA	6 (2.2)	9 (3.3)	Reference	
rs3745367	Genotype				
	GG	124 (44.6)	104 (37.7)	.672	0.899 (0.548-1.474)
	GA	109 (39.2)	130 (47.1)	.328	1.278 (0.782-2.089)
	AA	45 (16.2)	42 (15.2)	Reference	
	Allele				
	G	357 (64.2)	338 (61.2)	.306	0.880 (0.690-1.123)
	A	199 (35.8)	214 (38.8)	Reference	
	Dominant model				
	GG	124 (44.6)	104 (37.7)	.098	0.751 (0.535-1.054)
	AA+GA	154 (55.4)	172 (62.3)	Reference	
	Recessive model				
	GA+GG	233 (83.8)	234 (84.8)	.754	1.076 (0.681-1.701)
	AA	45 (16.2)	42 (15.2)	Reference	

CI, confidence interval; N, number; OR, odds ratio; SNP, single nucleotide polymorphism.

and genetic susceptibility to different serotypes of RA patients, and the results were shown in Table 2. However, the relationship of genetic heterogeneity between anti-CCP-positive and anti-CCP-negative RA patients was not statistically significant, as well as between RF-positive and RF-negative RA patients.

3.3 | Haplotype analysis

Six main haplotypes (CAG, CGG, GAA, GAG, GGA, and GGG) for *resistin* gene were determined by SHEsis software (Table 3). We found that the frequency of haplotype GAA was dramatically lower in RA

TABLE 2 Associations of *resistin* gene polymorphisms with risk of different serotypes of RA

SNP			Genotype n (%)				Allele n (%)		
Allele(M/m)	Clinical features	Group	MM	Mm	mm	*P* value	M	m	*P* value
rs1862513 C/G	anti-CCP	Positive	102 (43.6)	109 (46.6)	23 (9.8)	.831	313 (66.9)	155 (33.1)	.919
		Negative	18 (41.9)	22 (51.2)	3 (6.9)		58 (67.4)	28 (32.6)	
	RF	Positive	100 (43.7)	106 (46.3)	23 (10.0)	.711	306 (66.8)	152 (33.2)	.865
		Negative	20 (41.7)	25 (52.1)	3 (6.2)		65 (67.7)	31 (32.3)	
rs3745368 G/A	anti-CCP	Positive	174 (74.4)	54 (23.1)	6 (2.5)	.492	402 (85.9)	66 (14.1)	.805
		Negative	30 (69.8)	13 (30.2)	0 (0)		73 (84.9)	13 (15.1)	
	RF	Positive	170 (74.3)	53 (23.1)	6 (2.6)	.531	393 (85.8)	65 (14.2)	.921
		Negative	34 (70.8)	14 (29.2)	0 (0)		82 (85.4)	14 (14.6)	
rs3745367 G/A	anti-CCP	Positive	105 (44.9)	92 (39.3)	37 (15.8)	.883	302 (64.5)	166 (35.5)	.606
		Negative	18 (41.9)	17 (39.5)	8 (18.6)		53 (61.6)	33 (38.4)	
	RF	Positive	101 (44.1)	90 (39.3)	38 (16.6)	.939	292 (63.8)	166 (36.2)	.728
		Negative	22 (45.8)	19 (39.6)	7 (14.6)		63 (65.6)	33 (34.4)	

M, major alleles; m, minor alleles; n, number; SNP, single nucleotide polymorphism.

TABLE 3 Haplotype analysis of SNPs in *resistin* gene in RA patients and controls

Haplotype	Case [n(%)]	Control [n(%)]	$\chi 2$	*P* value	OR (95% CI)
rs1862513- rs3745367- rs3745368					
CAG	59.36 (0.107)	68.00 (0.123)	0.714	.398	0.852 (0.588-1.235)
CGG	288.82 (0.519)	258.60 (0.468)	3.146	.076	1.244 (0.977-1.583)
GAA	5.95 (0.011)	18.22 (0.033)	6.433	**.011**	0.317 (0.125-0.807)
GAG	118.47 (0.213)	114.72 (0.208)	0.056	.813	1.036 (0.774-1.385)
GGA	50.23 (0.090)	51.38 (0.093)	0.021	.884	0.970 (0.644-1.460)
GGG	9.34 (0.017)	18.68 (0.034)	3.241	.072	0.489 (0.221-1.082)

Global $\chi^2 = 11.657$, $P = .040$. Bold value means $P < .05$.
All the haplotype frequency <0.03 was ignored in the analysis.

patients when contrasted to normal controls (OR = 0.317, 95% CI: 0.125-0.807, *P* = .011).

4 | DISCUSSION

Rheumatoid arthritis is generally known as a chronic, complex autoimmune disease characterized by has complex genetic backgrounds.[19,20] Several studies have shown that pro-inflammatory cytokines play critical roles in the pathogenesis of multiple autoimmune diseases, including RA and systemic lupus erythematosus (SLE).[21,22] Recent investigations had indicated increased serum resistin level in RA patients when compared to the healthy controls.[15,16] Nevertheless, results from these studies were inconsistent, and several studies had suggested that no significant difference was found in the serum expression level of resistin between RA patients and healthy controls.[23,24] To further analyze serum resistin level in RA patients, a comprehensive meta-analysis was performed and the result indicated that serum resistin level in RA patients was significantly elevated.[25] In addition, the serum resistin levels were related to clinical disease activity, CRP and ESR in RA.[14,15] Similarly, a significant correlation between synovial fluid resistin level and several inflammatory markers of RA was also found in another study.[26] Therefore, resistin might be contributed to the inflammatory process in RA act as a significant mediator.

Several inflammation-associated SNPs including rs1862513, rs3745368, and rs3745367 in *resistin* gene, which located on chromosome 19p13, have been reported to relate with resistin concentration in some studies.[27-30] Therefore, we hypothesized that *resistin* gene polymorphisms might have a crucial role in RA development. However, we failed to found any significant relationship between *resistin* gene polymorphisms and RA risk in the present study, while the haplotype GAA was considered to be a significant protective haplotype for RA. Indeed, recent study implied that obesity might modestly contribute to RA and was associated with low-grade chronic inflammation.[5] A recent meta-analysis revealed that *resistin* rs1862513 variant may be related to obesity.[31] In another study, the authors suggested that the G allele of the −852A>G and haplotypes with G alleles at −852 and −420 were associated with higher circulating inflammatory biomarkers. This implied that *resistin* gene

polymorphisms might be associated with several inflammatory biomarkers secreted in serum/synovial from RA patients.[32] In addition, increasing evidences have shown that RA could be divided into disparate genetic subsets depend on the status of autoantibodies including anti-CCP and RF.[33,34] We also analyzed the potential associations between *resistin* gene polymorphisms and disparate serotypes of RA. Unfortunately, no significant associations were observed.

Several studies explored the role of *resistin* gene in cancer, diabetes, and autoimmune diseases had appeared in recent years.[35-38] Alharithy et al indicated that *resistin* rs1862513 heterozygous (CG) genotype and rs3745367 heterozygous (GA) genotype were significantly associated with an increased risk of colon cancer.[35] However, a previous study showed that *resistin* polymorphisms at rs1862513 and rs3745367 were not significantly linked to the risk of lung cancer.[36] A study by Thammakun et al suggested that *resistin* polymorphism at position +62 G>A (rs3745368) might increase the susceptibility to type 2 diabetes mellitus in Thais.[37] Another study demonstrated that *resistin* rs1862513 polymorphism might be of some significance in multiple sclerosis patients due to significantly higher *resistin* level was detected in GG genotype of *resistin* rs1862513 compared with CC carriers.[38] Hence, *resistin* gene polymorphisms might be involved in the development of autoimmune diseases by affecting the secretion and activity of inflammatory cytokines.

In conclusion, the results revealed that the frequency of haplotype GAA was significantly lower in RA patients, and *resistin* gene polymorphisms might affect the genetic predisposition of RA in the Chinese population. However, several limitations existed in our study might influence the accuracy of the results, for example, ethnic background, sample size, and patients with different disease activity, duration, and treatment. Therefore, further replication studies with larger sample size in different populations are still needed.

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